REMARKS/ARGUMENTS

Claim Status

Claims 1-9, 11-19, 21-22, 27-36, and 45-48 are under examination. Claims 10 and 20 are canceled. Claims 23-26 and 37-44 are withdrawn.

Applicants acknowledge the withdrawal of previously pending rejections as described in the Office Action on page 2.

In the remarks below, subheading numbers refer to the paragraph numbers of the Office Action.

Amendments to the Claims

Claims 1, 35-36, and 48 have been amended to correct grammatical or typographical errors. In addition, because the polypeptides encoded by SEQ NOs: 2 and 4 are the same, references to SEQ ID NO: 4 have been removed as duplicative.

Claims 1, 27-34, and 48 have been amended to specify that the recipient is a fish. This amendment is supported by the specification, *inter alia*, at paragraph [0001].

Claims 7 and 17 have been rewritten in independent form.

No new matter is added by these amendments. Amendment or cancellation of claims is to expedite prosecution and is not intended to indicate acquiescence with the position of the Office. Applicants expressly reserve the right to pursue any withdrawn and/or canceled subject matter in continuation or divisional applications.

35 U.S.C. § 112 Rejections

3. "Fragments"

Claim 20 stands rejected under 35 U.S.C. § 112, first paragraph because the invention is allegedly not enabled for "fragments." Applicants have canceled claim 20 because it recited redundant limitations to claim 1 as previously amended. Thus, this rejection is now moot.

5. "Recombinant protein fragments"

Claim 2 stands rejected under 35 U.S.C. § 112, second paragraph because the term "the recombinant protein fragments" allegedly lacks antecedent basis. Applicants have deleted the term "fragments" from claim 2, thus overcoming this rejection.

4. "Predetermined volume"

Claim 48 stands rejected under 35 U.S.C. § 112, second paragraph because the term "predetermined volume" is allegedly unclear. Applicants have deleted the term "predetermined volume," thus overcoming this rejection.

35 U.S.C. § 103 Rejections

Claims 1-22, 27-36, 45-46, and 48 were rejected as allegedly obvious over Fang et al. and a newly cited reference, Yang et al., with or without additional references. The Office states that "Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila*." The Office acknowledges that Fang et al do not teach oral administration, but argues that Yang et al. remedies this deficiency. The Office believes one of ordinary skill would have combined the description by Yang et al. of oral administration with the description by Fang et al. of an intraperitoneally administered vaccine, to arrive at the currently claimed invention. Applicants respectfully disagree for the reasons discussed below.

6. Fang et al. and Yang et al.

Claims 1-3, 5-6, and 10 were rejected as allegedly obvious over Fang et al. and Yang et al.

Yang et al. disclosed "an oral vaccine that includes a multiple-cell organism for use as food for an aquatic animal to be vaccinated, and a single-cell organism fed to, and as a result, bioencapsulated by, the multiple cell organism." Abstract. In other words, Yang et al. described transforming a single cell organism to express a recombinant antigen, feeding the recombinant single cell organism to a multiple cell organism such as a shrimp, and then feeding the multiple cell organism to a fish to deliver the antigen. Yang et al. did not disclose an oral vaccine comprising an isolated recombinant adhesin protein or isolated protein of any type. Indeed,

Yang et al. notes the desirability of oral vaccines, but teaches that oral vaccines are often ineffective:

> Preventing aquatic animal diseases by oral vaccination has several advantages over other methods: It is non-stressful, requires little labor, and can be applied at a large scale. However, many oral vaccines have been found ineffective as a result of failure to uptake sufficient dosage of antigen, poor antigen delivery and antigen degradation in the digestive tract. (col. 1, lines 9-16).

One of ordinary skill reading Yang et al. would not have been led to the current invention. Yang et al. disclosed only oral administration of a multicellular organism that contains a transformed and "bioencapsulated" single cell organism and attributes the efficacy of the "bioencapsulated" product to the "difficult antigen degradation in the digestive tract of the aquatic animal." Col. 2, lines 48-50. In view of Yang et al.'s disclosure, one of ordinary skill in the art would expect that an oral vaccine comprising an isolated recombinant protein, as presently claimed, would be ineffective. In contrast, the present inventors have provided an effective oral AHMA vaccine comprising isolated recombinant protein. *See* Example VIII of the specification.

The Fang et al. reference is cited for disclosure of blue gourami fish "intraperitoneally immunized with major adhesin, a 43 kDa OMP protein isolated from fish *Aeromonas hydrophila*, in the presence of Freund's complete adjuvant (FCA)." Abstract. Thus, Fang et al. teaches intraperitoneal immunization and, as recognized by the Office, did not teach or suggest an orally administered vaccine.

Contrary to the rationale proposed by the Office, one of ordinary skill reading these references would not have administered the intraperitoneal adhesin preparation described by Fang et al. using an oral route, because Yang et al. teaches that oral vaccines have been found ineffective as a result of failure to uptake sufficient dosage of antigen, poor antigen delivery, and antigen degradation in the digestive tract.

Moreover, even if, *arguendo*, one did combine the intraperitoneally administered protein of Fang et al. with the method of Yang et al., the result still would not be an oral vaccine comprising an isolated recombinant AHMA protein and capable of effecting immunization of a

fish against *Aeromonas hydrophila,* as now claimed. At best, the combination of Fang et al. and Yang et al. proposed by the Office might teach transforming a single cell organism with a recombinant adhesin gene, feeding the single cell organism transformed to express the recombinant protein to a multiple cell organism, and then feeding the multiple cell organism to a fish. This combination does not suggest the present invention.

Because neither Fang et al. nor Yang et al., alone or in combination, teach or suggest the oral administration of an isolated recombinant protein, Applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

8. Fang et al., Yang et al., and Calanchi et al.

Claims 7-9 were rejected as allegedly obvious over Fang et al., Yang et al., and Calanchi et al. The Office relied on Calanchi et al. for disclosure of a thickening agent, e.g., carboxymethylcellulose. Calanchi et al. described pharmaceutical formulations for human consumption.

However, the description in Calanchi would not have suggested the invention of claim 7. The present invention teaches that the oral vaccine comprising a binding agent achieves a "particulate consistency." [0045]. In contrast, Calanchi et al. discloses a formulation that may contain carboxymethylcellulose but explicitly avoids precipitation and particle formation. Calanchi et al. describes particle formulation as a disadvantage of the prior art:

> [W]hen the bag contents are poured as usual into water, milk, or fruit juices, microcapsules precipitate to the glass bottom or float on the liquid surface, sticking to the glass wall because of their hydrorepellancy. This causes a considerable inaccuracy in the drug dosage in addition to a poor compliance of the patient, who can see floating particles or has a scraping feeling in the mouth and throat when swallowing the final content of the glass, with its mass of precipitated particles. The addition to the formulation of thickening agents might have delayed or even eliminated microcapsule separation, but has been found to give particularly negative results, because in contact with water these substances form clots which are dissolved slowly only under a vigorous mechanical agitation. (col. 2, lines 12-27).

A particulate-free formulation, such as that suggested in Calanchi, would not be useful in the present invention. Because the formulation described in Calanchi et al. is explicitly does not have a particulate consistency, Calanchi et al. does not teach or suggest the binding agent limitation as claimed. Moreover, the description in Calanchi et al. does not remedy the basic deficiencies of Fang et al. and Yang et al. discussed above.

7. Fang et al., Yang et al., and Chen et al.

Claim 4 was rejected as allegedly obvious over Fang et al., Yang et al., and Chen et al. The Office relies on Chen et al. for the disclosure of palm oil. However, Chen et al.'s disclosure of palm oil (col. 6, line 42) does not overcome the deficiencies of Fang et al. and Yang et al. described above.

9. Fang et al., Yang et al., and Wang et al.

Claims 11-12, 15-16, 20, 27-32, 35-36, and 48 were rejected as allegedly obvious over Fang et al., Yang et al., and Wang et al. The Office relies on Wang et al. for disclosure of the *Ichthyophthirius multifiliis* antigen. Wang et al.'s disclosure of the *Ichthyophthirius multifiliis* antigen does not overcome the deficiencies of Fang et al. and Yang et al. described above. Furthermore, Wang et al., like Fang et al., is limited to intraperitoneal (injection) administration. *See* Abstract.

12. Fang et al., Yang et al., and Wolf-Watz et al.

Claims 21 and 33-36 were rejected as allegedly obvious over Fang et al., Yang et al., and Wolf-Watz et al. The Office relies on Wolf-Watz et al. for the disclosure of guppy reovirus. However, Wolf-Watz et al.'s disclosure of guppy reovirus (col. 6, line 61) does not overcome the deficiencies of Fang et al. and Yang et al. described above.

13. Fang et al., Yang et al., and Morinigo et al.

Claim 22 was rejected as allegedly obvious over Fang et al., Yang et al., and Morinigo et al. The Patent relies on Morinigo et al. for disclosure of "*Vibrio alginolyticus* and

Photobacterium damselae subsp. Piscicida antigens." However, Morinigo et al.'s disclosure of particular antigens does not overcome the deficiencies of Fang et al. and Yang et al. described above.

10, 11, 14, 15. Other combinations

Claims 13-16, 17-19, and 45-46 were rejected as allegedly obvious over various combinations of the references discussed above:

Claims 13-16 were rejected as allegedly obvious over Fang et al., Yang et al., Wang et al., and Chen et al. Office Action at ¶ 10.

Claims 17-19 were rejected as allegedly obvious over Fang et al., Yang et al., Wang et al., and Calanchi et al. Office Action at ¶ 11.

Claim 45 was rejected as allegedly obvious over Fang et al., Yang et al., Wang et al., and Wolf-Watz et al. *Id.* at ¶ 14.

Claim 46 was rejected as allegedly obvious over Fang et al., Yang et al., Wang et al., and Morinigo et al. *Id.* at ¶ 15.

For the reasons stated above, none of the combinations teach or suggest the present invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 202-481-9900.

Respectfully submitted,

Dana Buschmann

Date: Jan 25, 2008

Dana Buschmann
Reg. No. 54,567

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 202-481-9900
Fax: 415-576-0300
Attachments

61230949